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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,182	06/11/2001	Daniel C. Liebler	204931US-20	1234

22850 7590 12/29/2004

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EXAMINER

SODERQUIST, ARLEN

ART UNIT	PAPER NUMBER
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1743

DATE MAILED: 12/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/877,182	Applicant(s) LIEBLER ET AL.	
	Examiner Arlen Soderquist	Art Unit 1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-48 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,10-16,18,23-35,37 and 40-48 is/are rejected.
- 7) ☒ Claim(s) 4,6-9,17,19-22,36,38 and 39 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

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1. Claim 29 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The means for producing the mass spectra is not part of the claimed system and it does not appear that the type of mass spectrum affects any of the claimed means in a way that would further define the structure of the respective means.

2. Claims 13, 26, 31, 44 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what the basis is for automatic specification of spectral characteristics or their relationship: ion type such as peptide or oligonucleotide, means of generating the ions such as MALDI or electrospray, the type of mass spectrometer or some other basis. On page 16 of the October 18, 2004 response, applicant points out that the parameters are entered by the user which creates a clear question of what constitutes automatically specifying if the user is required to input the parameters. For examination purposes a program that is set to look for certain relationships based on a known ion series such as an alkane fragmentation series is considered to be within the claim scope.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 13, 28-29, 31, 33-35, 37, 43-44 and 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Dromey. In the paper Dromey presents a simple index for classifying mass spectra with applications to fast library searching. A simple ion series-related index (scoring system) was developed for classifying mass spectra. The index restricts the choice of molecular classes to which a spectrum may belong. Intraclass variations can be correlated with structural differences, while interclass variations are derived from the influence of different functional groups. The specificity of the index makes it ideal for structuring and searching mass spectral libraries. A library search scheme which retains the class definition of the file and still yields close to an order of magnitude reduction in the search space is described.

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The index is called a series displacement index (SDI) and is described on page 1465. This index includes a structural relationship term d_m that must be zero or positive with integral values that are less than 14 and a normalized percentage contribution to the total ion current of the m th ion intensity in the spectrum I_m . Beginning on page 1467, this scoring system is taught as applied to matching an unknown with members of a library. The process is shown in figure 6 the paragraph bridging pages 1468-1469 teaches the implementation of this system on a PP11/45 computer which would have had the graphical interface in addition to the computer readable medium.

5. Claims 1-3, 10, 12-13, 15-16, 23, 25-26, 28-31, 33-35, 37, 40, 43-44 and 46-48 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hines. In the paper Hines teaches a pattern-based algorithm for peptide sequencing from tandem high energy collision-induced dissociation mass spectra. A new strategy is reported for extracting complete and partial sequence information from collision-induced dissociation (CID) spectra of peptides. CID spectra are obtained from high energy CID of peptide molecular ions on a four-sector tandem mass spectrometer with an electro-optically coupled microchannel array detector. A peak detection routine reduces the spectrum to a list of peak masses and peak heights, which is then used for sequencing (preprocessing). The sequencing algorithm was designed to use spectral data to generate sequence fits directly rather than to use data to test the fit of series of sequence guesses. The peptide sequencing algorithm uses a pattern based on the polymeric nature of peptides to classify spectral peaks into sets that are related in a sequence-independent manner. It then establishes sequence relationships among these sets. Peak detection from raw data takes 10-20 seconds, with sequence generation requiring an additional 10-60 seconds on a Sun 3/60 work station. The program is written in the C language to run on a Unix platform. The principal advantages of this method are in the speed of analysis and the potential for identifying modified or rare amino acids. The algorithm was designed to permit real-time sequencing but awaits hardware modifications to allow real-time access to CID spectra. Table 1 shows the principle ions automatically used in the algorithm (also see the discussion of the sequencing algorithm starting on page 328). Figure 1 shows an ion series. Scoring in the sequencing routine is discussed in the paragraph starting on page 329.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
 2. Ascertaining the differences between the prior art and the claims at issue.
 3. Resolving the level of ordinary skill in the pertinent art.
 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
7. Claims 14, 27, 32 and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hines as applied to claims 1, 15, 28 and 34 above, and further in view of Yates (*Analytical Chemistry* **1995**, 67, 1426-1436). Hines does not teach adjusting the parameters of the mass spectrometer in response to the spectral score.

In the paper Yates presents a method to correlate tandem mass spectra of modified peptides to amino acid sequences in the protein database. They developed a method to correlate uninterpreted tandem mass spectra of modified peptides, produced under low-energy (10-50 eV) collision conditions, with amino acid sequences in a protein. The fragmentation patterns observed in the tandem mass spectra of peptides containing covalent modifications is used to directly search and fit linear amino acid sequences in the database. Specific information relevant to sites of modification is not contained in the character-based sequence information of the databases. The search method considers each putative modification site as both modified and unmodified in one pass through the database and simultaneously considers up to three different sites of modification. The search method will identify the correct sequence if the tandem mass spectrum did not represent a modified peptide. This approach is demonstrated with peptides containing modifications such as S-carboxymethylated cysteine, oxidized methionine, phosphoserine, phosphothreonine, or phosphotyrosine. In addition, a scanning approach is used in which neutral loss scans are used to initiate the acquisition of product ion MS/MS spectra of doubly charged phosphorylated peptides during a single chromatographic run for data analysis with the database-searching algorithm. The searching algorithm is used to modify the mass

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spectrometer's acquisition parameters from a neutral loss scan to a product ion MS/MS scan as found on page 1428 in the first full paragraph. The approach described in this paper provides a convenient method to match the nascent tandem mass spectra of modified peptides to sequences in a protein database and thereby identify previously unknown sites of modification.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the ability to change the type of scan being acquired by the mass spectrometer as taught by Yates into the Hines device and method because of the ability to obtain to types of information during a single analysis experiment and gather information about the peptides related to modifications such as phosphorylation sites as shown by Yates.

8. Claims 5, 11, 18, 24, 41-42 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hines as applied to claims 3, 10, 16, 23, 37 and 40 above, and further in view of Kwok. Hines does not teach searching for and scoring each of the claimed types of ions.

Kwok discusses self-training interpretive and a retrieval system in computer-aided interpretation of mass spectra. A self-training system is described for computer interpretation of mass spectra which utilizes directly data of all available reference spectra, and does not require prior spectra-structure correlations of these data either by human or computer effort. The computer selects different classes of data known to have high structural significance, such as characteristic ions, series of ions, and masses of neutrals lost, from the unknown mass spectrum, and matches these against the corresponding data of all the reference spectra. The reference compounds of closest match in each data class are examined for common structural features; criteria were determined so that such features can be identified with ~95% reliability. Tests with 110 "unknowns" not represented in the reference file showed that extensive-to-complete structural information can be obtained, if spectra of related compounds are present in the reference file.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the different types of ions taught by Kwok into the device and method of Hines because of their ability to provide information in the characterization of unknowns as taught by Kwok.

9. Claims 4, 6-9, 17, 19-22, 36 and 38-39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the

limitations of the base claim and any intervening claims. The art of record fails to teach or fairly suggest the combination of limitations.

10. Applicant's arguments filed October 18, 2004 have been fully considered but they are not persuasive. Relative to the objection of claim 29, examiner asks how can a means for producing the mass spectra further define a system that does not include the means as a component? In other words since the system is not required to include a means for producing the mass spectra, there does not appear to be any difference in the claimed system with respect to the type of device used to obtain the mass spectra that are being analyzed. Relative to the clarity of the claims, examiner points out that automatically specifying a relationship seems to be inconsistent with a user being required to enter the relationships. It appears that the claims are really trying to claim selecting the relationships from user entered options rather than a process that does not need the input of a user (that is how the claims are being read by examiner). With respect to the art rejections, the claims are generic in nature and include situations in which a database is examined to match an experimental spectra with a known spectra or features of a known spectra as well as identifying features in a spectrum or spectra database based on relationships defined by a user. As such the arguments are not commensurate in scope with the instant claims. Thus applicant needs to look at the claims and limit them to the scope not covered by the art for situations that applicant's invention is/was not intended to be used (identifying structural features in a mass spectra indicative of the presence of moieties of known structure in a larger molecule of unknown structure?).

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose current telephone number is (571) 272-1265 as a result of the examiner moving to the new USPTO location. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, reading "Arlen Soderquist". The signature is fluid and cursive, with a large, stylized "S" at the end.

December 27, 2004

ARLEN SODERQUIST
PRIMARY EXAMINER